REMARKS

Before this Amendment, claims 13-19 were pending. By this Amendment, claims 13 and 14 have been canceled without prejudice to the Applicants' right to pursue those claims in continuing applications. Accordingly, claims 15-19 are now pending.

The rejections under 35 U.S.C. §112, second paragraph

In the Office Action dated March 9, 2009, containing a final rejection, claim 14 was rejected for indefiniteness.

Claim 14 has been canceled. Accordingly, it is respectfully requested that this rejection be withdrawn.

In the Office Action dated March 9, 2009, containing a final rejection, claim 15 was rejected for indefiniteness. The Office Action stated that there was insufficient antecedent basis for the recitation of "said human" in claim 15.

Claim 15 has been amended to recite "a" human rather than "said" human. Accordingly, it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §112, first paragraph

In the Office Action dated March 9, 2009, containing a final rejection, claims 13-20 were rejected for lack of enablement.

Although the Applicants do not agree with this rejection as it pertains to claims 13 and 14, claims 13 and 14 have been canceled in order to expedite prosecution of claim 15 and its dependent claims.

The Office Action reviewed some of the factors involved in an enablement analysis that are discussed in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). According to the Office Action, these factors lead to a conclusion of non-enablement.

The Applicants respectfully disagree. In broad terms, the Applicants' position is that the specification discloses that xenon protects against apoptosis in a well-recognized model system, apoptosis is known to occur in sepsis, and apoptosis occurs through common mechanisms in nearly all cell types. Therefore, the results obtained with xenon in the model system used in the specification can be extrapolated to sepsis. The Applicants' position is explained in more detail below, where the Applicants discuss the relevance of some of the Wand factors to this enablement rejection.

State of, or the amount of knowledge in, the prior art

The Office Action, at page 6, stated that "apoptosis is a complex series of cellular events." Although not explicitly stated, presumably the Office Action's position is that this complexity favors a conclusion that the present claims lack enablement.

The Applicants do not contest that apoptosis is complex. However, this complexity does not favor a conclusion of lack of enablement because it is not necessary to understand the complexity of apoptosis in order to practice the claimed invention. It is merely necessary to understand how to administer xenon to patients suffering from sepsis. Since xenon is a substance that is well known for other medical uses, methods of administering xenon are well known. Those skilled in the art would know how to adapt those methods without undue experimentation in order to administer xenon to treat patients suffering from sepsis.

Furthermore, the specification provides guidance as to how to administer xenon to treat sepsis. See, e.g., the paragraph bridging pages 6 and 7, where it is taught that xenon may be administered to treat sepsis directly into the intestine as a gas or by using a xenon-saturated salt solution.

Level or degree of predictability, or lack thereof, in the prior art

The Office Action, at page 4, stated that "Apoptosis is a complex mechanism where much is left unknown."

The Applicants do not disagree that apoptosis is complex, but wish to point out that the fact that apoptosis is complex and that much in still unknown about apoptosis does not weigh in favor of a conclusion of lack of enablement for the present claims. As discussed above, there is no need for those skilled in the art to understand all that is still unknown about apoptosis in order to administer xenon for the purposes recited in the present claims. All that is necessary is to follow the guidance of the present specification, in light of what is well known in the art.

Amount of guidance or direction provided by the inventor

The Office Action, in the sentence bridging pages 6 and 7, stated: "[T]here is a lack of guidance in the specification as to how one would extrapolate the cell based neuroprotection experiments to ... protecting against sepsis."

The Applicants respectfully disagree. Present claim 15 recites "reducing apoptotic cell death in endothelial cells of the intestine in sepsis." The experiments in the specification, when combined with well-known knowledge in the art, would be viewed by one of ordinary skill in the art as predicting success for the use of xenon to reducing apoptotic cell death in endothelial cells of the intestine in sepsis because:

- The experiments described in the specification were conducted using staurosporine treatment, a well known model system for apoptosis.
- Cell death that occurs in endothelial cells of the intestine during sepsis is known to be due to apoptosis.
- The results using the staurosporine model system would be expected to be applicable to endothelial cells of the intestine because apoptosis is known to occur by similar mechanisms in different cell types.
- The experiments described in the specification show that xenon completely protected against apoptotic cell death in the model system used; thus, xenon would be expected to protect endothelial cells of the intestine from apoptotic cell death during sepsis.

The fact that sepsis operates by common mechanisms in different cell types means that one can extrapolate success in protecting against apoptotic cell death in one cell type to success in protecting against apoptotic cell death in another cell type. Therefore, the successful protection against apoptotic cell death shown by xenon in the model system used in the examples of the present specification predicts that xenon will protect against apoptotic cell death in sepsis.

The considerations discussed above will now be discussed in more detail.

Staurosporine treatment is a well-recognized model system for apoptosis

As disclosed in the specification, at page 11, staurosporine is "generally considered a model apoptosis inducer."

> (B) Induction of apoptosis
> Apoptosis was induced using staurosporine. Staurosporine is an antibiotic originally discovered by Omura et al., J. Antibiot. 30 (1977), 275. It is generally considered a model apoptosis inducer when present in micromolar concentration (Tamaoki et al., BBRC 135 (1986), 397; Nakano et al., J. Antibiot. 40 (1987), 706; Ruegg and Burgess, TIPS 10 (1989), 218; Bertrand et al., Exp. Cell Res. 211 (1994), 314; Wiesner and Dawson, CLAO J. 24 (1996), 1418; Boix et al., Neuropharmacology 36 (1997), 811; Kirsch et al., J. Biol. Chem. 274 (1999), 21155; Chae et al., Pharmacol. Res. 42 (2000), 373; Heerdt et al., Cancer Res. 60 (2000), 6704; Bijur et al., J. Biol. Chem. 275 (2000), 7583; Scarlett et al., FEBS Lett. 475 (2000), 267; Tainton et al., BBRC 276 (2000), 231; Tang et al., J. Biol. Chem. 275 (2000), 9303; Hill et al., J. Biol. Chem. 276 (2001), 25643). Cells were seeded in 24-well plates at 6 days

See, e.g., Hill et al., 2001, J. Biol. Chem. 276:25643-25646[1], page 25643, right column: "Staurosporine has been widely used as an inducer of apoptosis."

See also Bijur et al., 2000, J. Biol. Chem. 275:7583-7590[2], (Bijur) page 7586, right column: "Staurosporine is one of the most commonly used agents to experimentally induce apoptosis, and apoptosis occurs in essentially all cell types exposed to appropriate concentrations of staurosporine." [underscoring added]

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[1] A copy of this publication was provided as Exhibit A with the Amendment filed January 6, 2009.

[2] A copy of this publication was provided as Exhibit B with the Amendment filed January 6, 2009.

See also Andersson et al., 2000, Invest. Ophthalmol. Visual Sci. 41:2623-2632 (Exhibit A), page 2624,left column: "In this study, activation of several caspases was detected in several bovine lens epithelial cells (BLECs) during staurosporine-induced apoptosis, a commonly used way of provoking programmed cell death." [underscoring added]

See also Bertrand et al., 1994, Exp. Cell Res. 211:314-321 (Exhibit B), page 314, paragraph bridging left and right columns: "Until now, however, the induction of apoptosis *in vitro* has been limited to certain cell models, suggesting that these cells are at least partially programmed for apoptosis. Although those systems provide important models for studying programmed cell death, the finding of a common stimulus may prove to be useful in understanding the biochemical chain of events involved in apoptosis. In the present study we show that staurosporine induces apoptosis in a variety of human tumor cell lines ..."

Cell death that occurs in endothelial cells of the intestine during sepsis is known to be due to apoptosis

The art teaches that apoptosis in intestinal endothelial cells plays an important role in sepsis. See, e.g., Power et al., 2002, Shock 18:197-211 (Exhibit C), page 206, right column:

> We have mentioned how bacterial translocation from the gut to the systemic circulation via the lymphatics may be a crucial step in the establishment of SIRS/MODS[3] [part of sepsis]. This naturally presupposes that either gut mucosal epithelial layer or submucosal endothelial integrity is somehow compromised. There is substantial evidence, already cited, that endothelial function is altered by increased apoptosis, but there is increasing proof that LPS modulates epithelial cell apoptosis, perhaps promoting the likelihood of a mucosal breach.

[3] "SIRS" is an acronym for systemic inflammatory response syndrome, another name for apoptosis. See the entry for sepsis from Medline Plus (cited in the present Office Action).

See also Oberholzer et al., 2001, FASEB J. 15:879-892 (Oberholzer) (Exhibit D), page 880, left column:

> [T]here is rapidly developing evidence to suggest that increased apoptotic processes may play a determining role in the outcome to sepsis syndromes. ... Therapeutic efforts at modulating the apoptotic response, particularly by interfering with cell signaling pathways that lead to caspase-mediated apoptosis, represent an attractive therapeutic target for the septic patient.

See also Oberholzer, page 888, left column, where it is stated that targeting caspases is an appropriate schema for treating sepsis:

> A more appropriate schema [for treating sepsis] is to target directly the specific intracellular pathways and effectors leading to sepsis-induced cell death, such as the caspases or PARP, whose activation may be the common product of mitochondrial or cytosolic apoptotic pathways.

See also Oberholzer, page 888, left column: "Therapeutic efforts aimed at blocking cell signaling pathways leading to apoptosis may represent a new therapeutic target for the critically ill patient with sepsis or systemic inflammatory response syndromes."

Thus there is abundant evidence that the art understands that apoptotic cell death occurs in sepsis and that modifying apoptosis is a promising approach for the treatment of sepsis.

Apoptosis is known to occur by similar mechanisms in different cell types

Apoptosis is known to involve similar mechanisms of caspase activation, nuclear and cellular breakdown, DNA fragmentation, and other biochemical events that are common to a wide variety of species and tissues. See, e.g., Gerschenson & Botello, 1992, FASEB J. 6:2450-2455 (Exhibit E), abstract, page 2450:

Apoptosis is a type of cell death that plays an important role in early development and growth of normal adult tissues. It is regulated by physiological stimuli and is present in many species and tissues. The main morphological characteristics are nuclear fragmentation and cellular breakdown in apoptotic vesicles. Internucleosomal DNA fragmentation is an important biochemical feature that is the result of a yet to be isolated endonuclease activity. [underscoring added]

See also the entry for "Apoptosis" in Wikipedia, http://en.wikipedia.org/wiki/Apoptosis (Exhibit F):

Apoptosis (pronounced /□æpəp□toʊsɨs/) is the process of programmed cell death (PCD) that may occur in multicellular organisms. Programmed cell death involves a series of biochemical events leading to a characteristic cell morphology and death, in more specific terms, a series of biochemical events that lead to a variety of morphological changes, including blebbing, changes to the cell membrane such as loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. (See also Apoptosis DNA fragmentation.)

...

Many pathways and signals lead to apoptosis, but there is only one mechanism that actually causes the death of a cell. [underscoring added; citations omitted]

See also U.S. Patent No. 6,180,402 (Exhibit G), col. 1, l. 46, to col. 2, l. 4:

Apoptosis is the term used to describe a type of cellular death that occurs in many tissues as a normal physiological process. Apoptosis is a morphologically distinct form of cell death that plays an important role during normal development, differentiation, and homeostasis or turnover of tissues. Also called "programmed cell death," this form of cellular demise involves the activation in cells of a built-in genetic program for cell suicide by which cells essentially autodigest.

The goal of apoptosis is to attain an orderly disintegration of cells into structures suitable for phagocytosis. Morphologically, apoptosis is begun by loss of contact with neighboring cells and smoothening of the cell surface (vesicle formation on the cell surface and membrane "blebbing"). It is further characterized by the concentration of the cytoplasm, endonuclease activity-associated chromatin condensation and pyknosis, and segmentation of the nucleus. The orderly disintegration of cells also includes the degradation of genomic DNA into

> nucleosomal fragments and cellular fission to form apoptotic bodies. The nucleosome units of the resulting DNA fragments are about 180-200 bases in size. The final fragments of apoptotic body cells are phagocytosed by neighboring cells. The remnants of these dead cells are then cleared almost without a trace by neighboring phagocytic cells, without resulting in inflammation or scarring.

See also U. S. Patent No. 6,184,210 (Exhibit H), col. 1, ll. 36-42:

> There are a number of morphological changes shared by cells experiencing regulated cell death, including plasma and nuclear membrane blebbing, cell shrinkage (condensation of nucleoplasm and cytoplasm), organelle relocalization and compaction, chromatin condensation and production of apoptotic bodies (membrane enclosed particles containing intracellular material).

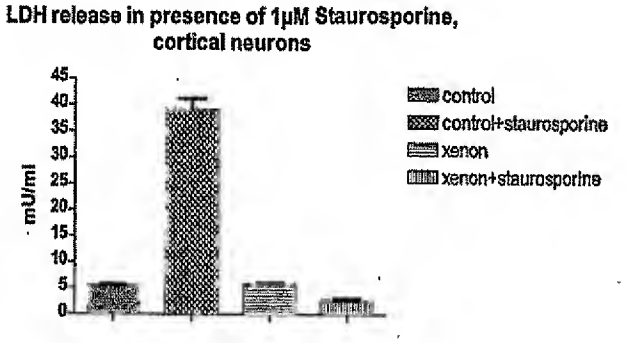
See also U. S. Patent No. 6,403,792 (Exhibit I), col. 1, ll. 28-38:

> *Apoptosis* appears to be a carefully controlled series of cellular events which ultimately leads to death of the cell. This process for elimination of unwanted cells is active and requires expenditure of cellular energy. The morphological characteristics of *apoptosis* include cell shrinkage and loss of cell-cell contact, condensation of nuclear chromatin followed by fragmentation, the appearance of membrane ruffling, membrane blebbing and apoptotic bodies. At the end of the process, neighboring cells and macrophages phagocytose the fragments from the apoptotic cell. The process can be very fast, occurring in as little as a few hours.

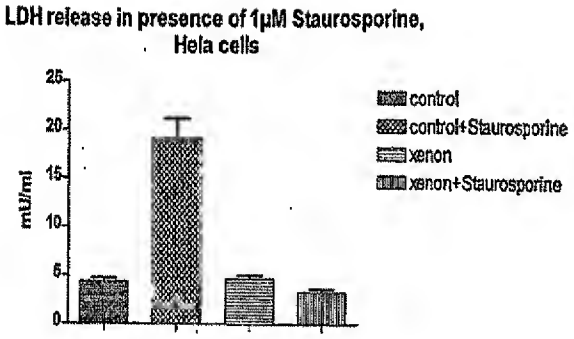
That "apoptosis occurs in essentially all cell types exposed to appropriate concentrations of staurosporine" (see quote from Bijur above) strongly suggests that staurosporine acts on common apoptotic mechanisms that are present in essentially all cell types. That xenon can protect against the action of staurosporine implies that xenon must also be acting on those common mechanisms. Since xenon is acting on common apoptotic mechanisms, the effects of xenon seen in the experiments disclosed in the present application can be extrapolated to apoptosis in other settings, including endothelial cells of the intestine during sepsis.

Xenon completely protected against apoptosis

The protective effect of xenon in the model system used in the present application was essentially complete. See Figure 1 of the present application

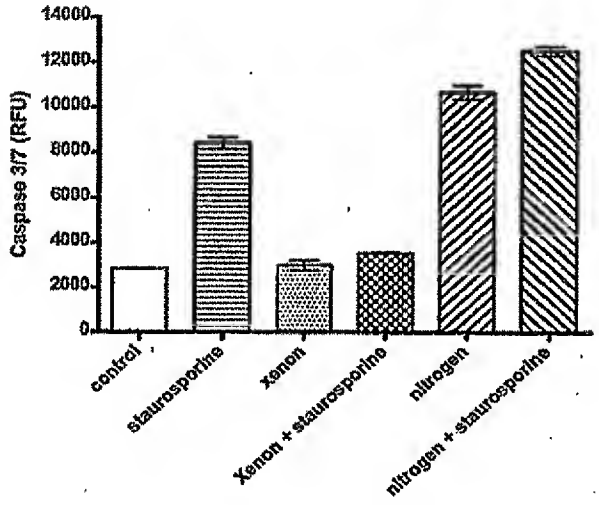


and Figure 2



Furthermore, the data disclosed in the present application show that xenon almost completely inhibited the activity of caspases 3 and 7. This is especially noteworthy in view of the passage from Oberholzer quoted above indicating that the art believes that caspases are attractive targets for the treatment of apoptotic cell death in sepsis.

The data pertaining to inhibition of caspases 3 and 7 are summarized in Figure 4 of the present application. Comparison of the fourth bar from the left (representing caspase 3 and 7 activity in the presence of xenon and staurosporine) with the first bar from the left (representing background caspase 3 and 7 activity) indicates that xenon prevents the level of caspase 3 and 7 activity after treatment with staurosporine from rising more than an insignificant amount above the background level. This can be contrasted with the second bar from the left, which shows that caspase 3 and 7 activity rises greatly after staurosporine treatment in the absence of xenon.



Caspases, and in particular caspases 3 and 7, are among the key players in apoptosis and are responsible for many of the events that occur during programmed cell death. The measurement of their activity serves as a biochemical marker for apoptosis.

See, e.g., Taylor et al., Nature Reviews (Molecular Cell Biology), 2008, 231-241[4] (Taylor), page 233:

[4] Taylor was cited in the Office Action dated October 8, 2008.

> Irrespective of the actual route to caspase activation, all pathways lead to the activation of the major effector caspases, caspase-3, caspase-6 and caspase-7, and these enzymes carry out much of the proteolysis that is seen during the demolition phase of apoptosis.

See also Taylor, page 236:

> Caspases also target many proteins that are involved in essential housekeeping functions within the cell. Proteins that function in transcription (for example, nuclear factor of activated T cells (NFAT), nuclear factor-κB (NFκB) p50 and p65, and La ribonucleoprotein) and translation (for example, the translation initiation factors eIF2a, eIF3, eIF4 and the β-subunit of the nascent polypeptide-associated complex (βNAC)) come under caspase-mediated attack during apoptosis and ribosomal RNA is also degraded. Genomic DNA becomes extensively hydrolysed and the Golgi, ER and mitochondrial networks undergo fragmentation. Indeed, all of the major cell organelles become extensively remodelled during apoptosis and, once again, caspases orchestrate much of this (Fig. 3). [citations omitted]

See also Bijur, page 7584, left column: "The enzymes that ultimately carry out the command for apoptosis are the cysteine proteases known as caspases. ... [T]he measurement of caspase-3 activity can serve as a biochemical marker for the execution phase of apoptosis."

The ability of xenon to inhibit caspases 3 and 7 in the model system used in the present application argues that the results seen in that model system can be extrapolated to other systems where apoptosis occurs, including endothelial cells of the intestine during sepsis.

Presence or absence of working examples

At page 7, the Office Action stated: "The specification fails to provide specific data and working embodiments with respect to ... protecting endothelial cells of the intestine in sepsis."

The Applicants wish to point out that there is no requirement that the specification provide working examples that precisely track the claimed invention in order to satisfy the enablement requirement. *In re Strahilevitz*, 668 F. 2d 1229, 1232, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982): "[Working] examples are not required to satisfy section 112, first paragraph."

Furthermore, the Applicants do provide working examples that demonstrate blockage of apoptosis by xenon. As discussed above, combined with knowledge in the art relating to apoptosis in general and the role of apoptosis in sepsis, this is enough to enable the present claims.

Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

In the paragraph bridging pages 7 and 8, the Office Action stated, with respect to patients suffering from sepsis:

> Clearly such patients will also be treated with conventional therapeutic agents and as taught by Remingtons [sic] it is unpredictable how multiple drugs are going to interact. Without any guidance on how to extrapolate the data provide by Applicant or drug interactions with drugs used in the treatment of sepsis ... essentially one of ordinary skill in the art has to figure out how to do this themselves. As a result, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to see if the method of ... protecting endothelial cells of the intestine in sepsis actually works.

The Applicants respectfully submit that there is no requirement that the specification teach how to administer xenon with any other drugs in order to meet the enablement requirement because the present claims do not recite the administration of xenon with any other drugs. A patent must only enable what is claimed; there is no need to enable what is not claimed. "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the

full scope of the claimed invention without 'undue experimentation.'" [underscoring added] *Genentech, Inc. v. Novo Nordisk A/S*, 108 F. 3d 1361, 1365, 42 U.S.P.Q. 2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F. 2d 1557, 1561, 27 U.S.P.Q. 2d 1510, 1513 (Fed. Cir. 1993)).

Other matters

At page 8, the Office Action argued that the specification does not enable the recitation of the term "preventing" in the claims. The Applicants do not agree. Nevertheless, in the interests of expediting prosecution, all claims reciting "preventing" have been canceled.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The time for responding to the Office Action was set for June 9, 2009. Therefore, it is believed that this response is timely. If this is in error, please treat this response as containing a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this paper and charge any corresponding fees to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Commissioner is authorized to charge Kenyon &

Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

Date: June 5, 2009

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